Altered perspective-dependent brain activation while viewing hands and associated imitation difficulties in individuals with autism spectrum disorder

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ABSTRACT

Background: Individuals with autism spectrum disorder (ASD) appear to have a unique awareness of their own body, which may be associated with difficulties of gestural interaction. In typically developing (TD) individuals, the perception of body parts is processed in various brain regions. For instance, activation of the lateral occipito-temporal cortex (LOTC) is known to depend on perspective (i.e., first- or third-person perspective) and identity (i.e., own vs. another person's body). In the present study, we examined how perspective and identity affect brain activation in individuals with ASD, and how perspective- and identity-dependent brain activation is associated with gestural imitation abilities.
Methods: Eighteen young adults with ASD and 18 TD individuals participated in an fMRI study in which the participants observed their own or another person's hands from the first- and third-person perspectives. We examined whether the brain activation associated with perspective and identity was altered in individuals with ASD. Furthermore, we identified the brain regions the activity of which correlated with gestural imitation difficulties in individuals with ASD.
Results: In the TD group, the left LOTC was more strongly activated by viewing a hand from the third-person perspective compared with the first-person perspective. This perspective effect in the left LOTC was significantly attenuated in the ASD group. We also observed significant group differences in the perspective effect in the medial prefrontal cortex (mPFC). Correlation analysis revealed that the perspective effect in the inferior parietal lobule (IPL) and cerebellum was associated with the gestural imitation ability in individuals with ASD.
Conclusions: Our study suggests that atypical visual self-body recognition in individuals with ASD is associated with an altered perspective effect in the LOTC and mPFC, which are thought to be involved in the physical and core selves, respectively. Furthermore, the gestural imitation difficulty in individuals with ASD might be associated with the altered activation in the IPL and cerebellum, but not in the LOTC. These findings shed light on common and divergent neural mechanisms underlying atypical visual self-body awareness and gestural interaction in ASD.

1. Introduction

Autism spectrum disorder (ASD) is a range of neurodevelopmental conditions characterized by difficulties in social communication and interaction, as well as restricted, repetitive behaviors, interests, or activities (American Psychiatric Association, 2013). The difficulties in social communication and interaction encompass both verbal and nonverbal behaviors. With respect to the nonverbal behaviors, individuals with ASD experience difficulties recognizing another person's action (Cossu et al., 2012) and interacting with another person using their bodies (e.g., reciprocal imitation [Gergely, 2001; Nadel, 2002; Williams et al., 2004]).

In addition to social-communicative difficulties, individuals with ASD have been reported to present with atypical self-recognition abilities (Lombardo and Baron-Cohen, 2011; Uddin, 2011). The self includes the physical self (i.e., the external features, such as those of the body) and the psychological self (i.e., the internal features, such as the individual traits). Although several researchers have proposed that atypicality is limited to the psychological self (Lombardo and Baron-Cohen, 2011; Uddin, 2011), recent behavioral studies have reported that individuals with ASD have unique awareness of their bodies, a component of the physical self that has a more primitive function than social interaction (Asada et al., 2017; Cascio et al., 2012; Kern et al., 2006; Paton et al., 2012). For instance, estimation of own body size is less accurate in individuals with ASD than in typically developing (TD) individuals (Asada et al., 2017). The physical self is thought to contribute to social development (Neisser, 1988; Sugiura, 2013). Therefore, altered self-body recognition might be the cause of atypical bodily interaction in ASD individuals. If this is the case, which neural mechanism is associated with atypical self-body recognition in ASD? In the present study, we focused our investigation on visual processing for self-body recognition in ASD.

Previous neuroimaging studies of TD individuals have found that perception of the physical self involves a distributed network of brain regions including the lateral occipito-temporal cortex (LOTC), superior temporal sulcus (STS), inferior parietal lobule (IPL), and inferior frontal gyrus (IFG) (Sugiura, 2013; Uddin et al., 2007; Uddin, 2011). While multi-sensory inputs can drive this network (e.g., proprioception), a detailed network for visual processing has been proposed: visual features of a body are initially processed in the LOTC and then sent to other nodes (Gazzola and Keysers, 2009; Taylor et al., 2007). The LOTC contains a region (the extrastriate body area [EBA]) that is more strongly activated by viewing body parts relative to viewing other objects such as scenes or tools (Downing et al., 2001). Moreover, adjacent to the EBA, there is a region more strongly activated by the upper limbs relative to other body parts such as the trunk and lower limbs (Bracci et al., 2010; Orlov et al., 2010; Peelen and Caramazza, 2010). The LOTC is also thought to process several visual features associated with self-body recognition. Specifically, LOTC activation is modulated by perspective (i.e., first- vs. third-person perspective) and identity (i.e., own body vs. the body of another person) (Chan et al., 2004; Myers and Sowden, 2008; Saxe et al., 2006). These findings suggest that the LOTC is involved in the categorization of body parts (e.g., hand or foot) and differentiation of the owner of these body parts (i.e., own hand vs. another person's hand). These findings suggest that LOTC dysfunction is a possible neural mechanism underlying the atypical awareness of the visual self-body in individuals with ASD.

In previous fMRI studies, we have found that, although TD and ASD adults show similar LOTC selective responses to body parts (Okamoto et al., 2014, 2017), the EBAs of adults with ASD show atypical responses when observing another person's action contingent on self-action (Okamoto et al., 2014). These findings indicate that lower-level LOTC functions such as object categorization may be intact in adults with ASD, whereas higher-order functions such as detecting social contingency are perturbed. Therefore, we expected that the processing of perspective and identity of bodies in this area, more complex than

simple categorization, might also be dysfunctional in adults with ASD. However, to the best of our knowledge, no study to date has examined how perspective and identity of bodies affect LOTC activation in individuals with ASD.

In the present study, we used fMRI to examine brain activation during an experimental task in which young male adults with ASD and TD individuals observed their own or another person's hands from the first- and third-person perspectives. To evaluate LOTC activation, we initially depicted the upper-limb-sensitive (ULS) region within the LOTC and then examined the sensitivity of this region to hand viewing with different perspectives and identities. We predicted that the effects of perspective and identity on hand perception were different between young adults with and without ASD. We further explored if brain activation was associated with difficulties in bodily interaction in individuals with ASD, which allowed us to examine the nature of heterogeneity among ASD participants. In particular, as some individuals with ASD show a unique imitation error due to a failure to adopt another person's perspective (i.e., reversal error) (Ohta, 1987; Williams et al., 2004), atypical perspective-dependent brain activation might be associated with the severity of imitation difficulties in individuals with ASD. Although the perspective of observed action can affect the activation of brain regions beyond the LOTC (Jackson et al., 2006), it is not clear if such activation is associated with the imitation difficulties in individuals with ASD. To examine this possibility, we evaluated the imitation ability in ASD participants and depicted the brain regions the activity of which was correlated with it.

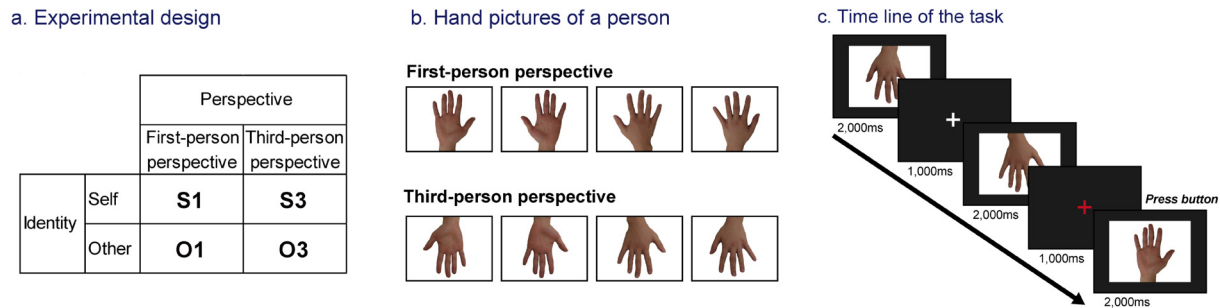## 2. Materials and methods

2.1. Participants

Eighteen young male adults with ASD (age, mean ± standard deviation [SD]: 28.2 ± 6.9 years) and 18 young male TD adults (age: 24.8 ± 5.0 years) participated in the study (Table 1). ASD participants were recruited from the outpatient department of the University of Fukui Hospital and diagnosed by a psychiatrist (H.K) based on the DSM-5 diagnostic criteria (American Psychiatric Association, 2013). To establish a DSM-5 diagnosis, H.K. applied the Diagnostic Interview for Social and Communication Disorders (DISCO) (Wing et al., 2002), which collects information about various developmental and behavioral features including social functioning and communication (Wing et al., 2002). TD individuals were recruited from the local community. Participants of both groups were excluded if they had a history of major

Table 1
Demographic data.

		TD group	ASD group	p-Values
Number		18	18	
Age		24.8 ± 5.0	28.2 ± 6.9	0.102
IQ	FSIQ	113.7 ± 8.6	109.2 ± 12.6	0.214
	vIQ	116.2 ± 12.6	112.9 ± 16.2	0.506
	pIQ	107.6 ± 7.5	104.8 ± 12.0	0.413
SRS		58.3 ± 26.5	110.7 ± 26.8	< 0.001
AQ	Total	17.7 ± 3.6	34.9 ± 5.0	< 0.001
	Social	3.0 ± 2.2	8.4 ± 1.5	< 0.001
	Attention switching	4.8 ± 1.6	7.5 ± 1.8	< 0.001
	Attention to detail	4.2 ± 2.4	5.4 ± 2.4	0.176
	Communication	2.1 ± 1.6	7.6 ± 1.8	< 0.001
	Imagination	3.6 ± 1.4	5.7 ± 2.4	0.004

TD: Typically developing, ASD: Autism spectrum disorder, Number: Number of participants, IQ: Intellectual quotient assessed by the Wechsler Adult Intelligence Scale, Third Edition (Wechsler, 1997), FSIQ: Full scale IQ, pIQ: Performance IQ, vIQ: Verbal IQ, SRS: Social responsive scale score (Constantino and Todd, 2005), AQ: Autism Spectrum Quotient (Baron-Cohen et al., 2001). Age and IQ, SRS, and AQ scores are shown as mean ± SD. The p values indicate the results of independent-samples t-tests that compared the ASD and TD groups.

fMRI task: Hand obeservation task

a. Experimental design

		Perspective	
		First-person perspective	Third-person perspective
Identity	Self	S1	S3
	Other	O1	O3

b. Hand pictures of a person

First-person perspective

Third-person perspective

c. Time line of the task

2,000ms
1,000ms
2,000ms
1,000ms
Press button
2,000ms

Fig. 1. fMRI hand observation task.
(a) Experimental design of the hand observation task. This design was also used in the hand identification task. (b) Representative pictures utilized in the present study. The same pictures were used in the hand identification task. (c) Task sequence of the hand observation task. Participants observed pictures and were asked to press a button as soon as a red cross appeared.

medical or neurological illness including epilepsy, significant head trauma, or a lifetime history of alcohol or drug dependence. We confirmed that all participants were right-handed by the Edinburgh Handedness Inventory (Oldfield, 1971).

We obtained intelligence quotient (IQ) scores using the Wechsler Adult Intelligence Scale-III (Wechsler, 1997). We also measured individual autistic traits by the Autism Spectrum Quotient (AQ) score (Baron-Cohen et al., 2001) and Social Responsiveness Scale (SRS) score (Constantino and Todd, 2005) in all participants. There were no group differences in age and full-scale IQ (FSIQ) (all p > 0.1, independent-samples $0D$), and the FSIQ scores of all participants were > 80 (Table 1). The total AQ and SRS scores were significantly higher in individuals with ASD than in TD individuals (all p < 0.001, independent-samples t-test) (Table 1).

Our protocol was in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the University of Fukui (Japan). Before participation, written informed consent was obtained from each participant. All methods were carried out in accordance with the approved protocol.

2.2. MRI parameters

All functional volumes were acquired using T2*-weighted gradient-echo echo-planar imaging (EPI) sequences using a 3-Tesla magnetic resonance imager (Discovery MR750; GE Healthcare, Milwaukee, Wisconsin, USA). Every volume consisted of 40 oblique slices, each 3.0 mm in thickness, with a 17% gap, in order to cover the entire cerebral and cerebellar cortex. The time interval between 2 successive acquisitions of the same slice (repetition time; TR) was 3000 ms with a flip angle (FA) of 90° and a 25 ms echo time (TE). The field of view (FOV) was 192 × 192 mm. The digital in-plane resolution was 64 × 64 pixels with a pixel dimension of 3.0 × 3.0 mm. A high-resolution anatomical T1-weighted image was also acquired by fast spoiled gradient recalled imaging sequence (TR = 6.38 ms; TE = 1.99 ms; FA = 11°; 256 × 256 matrix; 172 slices; voxel dimensions = 1 × 1 × 1 mm).

2.3. Experimental setup

Presentation of visual stimuli and response collection were conducted with the Presentation software (Neurobehavioral Systems, Berkeley, CA, USA) implemented on a Windows-based desktop computer. Visual stimuli were presented on a screen by a liquid-crystal display projector. Participants viewed the visual stimuli via a mirror attached to the head coil of the MRI scanner. Head motion was minimized by placing comfortable but tight-fitting foam padding around each participant's head.

2.4. Task procedures

The participants completed 2 fMRI and 2 behavioral tasks. During the fMRI tasks, the participants completed a hand observation task in which they were asked to observe their own or another person's hands from both the first- and third-person perspectives. To localize the ULS region in the LOTC, the participants performed a functional localizer task. In the behavioral tasks, we assessed imitation skills in the individuals with ASD and the ability to judge hand identity in all participants.

2.4.1. fMRI tasks

2.4.1.1. Hand observation task. We selected "hand" as the visual stimulus among the various body parts, because the hand is one of the most important body parts for social interaction. The participants observed photographs of self or another person's hands from the first- and third-person perspectives. Thus, this task involves a 2 (identity: Self hand [S]/Other hand [O]) × 2 (perspective: first-person perspective [1]/third-person perspective [3]) factorial design. The S1, S3, O1, and O3 conditions corresponded to self-hand from the first-person perspective, self-hand from the third-person perspective, other person's hand from the first-person perspective, and other person's hand from the third-person perspective, respectively (Fig. 1a).

To prepare the photo stimuli of the Other hand conditions, hand photographs of 4 male hand models were obtained with a digital camera. Four photographs were taken for each hand model, 1 of each the right palm, left palm, back of the right hand, and back of the left hand. The background color of all photographs was changed to white, and the matrix size of the photographs was changed to 3543 × 4724 pixels in the Adobe-Photoshop software (Adobe System Inc., San Jose CA, USA). Hand perspectives were manipulated by rotating the hand direction by 180°. In total, we prepared 8 photo stimuli (i.e., 4 photographs with the first-person perspective and 4 photographs with the third-person perspective) from each hand model (Fig. 1b). For the Other hand conditions, the hand photographs of 1 of the 4 hand models were presented. The photo stimuli of the Self hand conditions were prepared via the same procedure, using photographs of each participant's hands.

Each participant completed 4 runs, each of which employed a conventional block design. In each run, there were 23 blocks, 12 s each. Specifically, within a run, each condition block (S1, S3, O1, and O3) was repeated 4 times (4 conditions × 4 times = 16 blocks), and the remaining 7 blocks (1st, 2nd, 7th, 12th, 17th, 22nd, and 23rd blocks) were fixation-only baseline conditions. In each condition block (S1, S3, O1, and O3), 4 different photographs (i.e., the right palm, left palm, back of the right hand, back of the left hand) were successively presented for 2000 ms with a 1000 ms interstimulus interval (ISI). Therefore, each photograph was presented 4 times per run (once per block × 4 blocks = 4 times), and 16 times per task (4 runs × 4

times = 16 times). A fixation cross was presented during the baseline condition block and ISI of each condition, and the color of the fixation cross was changed from white to red for 1000 ms once per block. The viewing angles of the photographs were 7.4° × 9.9°. Participants in the MR scanner were unable to see their own hands during this task.

We aimed to measure the brain activation associated with visual processing of perspective and hand identity. Therefore, participants were not required to perform any task associated with visual features of the hand (identity and perspective), because the judgment of identity or perspective might recruit unexpected cognitive processes such as motor imagery or memory. Instead, the participants were asked to press a button with their right index finger when the red fixation cross was presented to hold the participants' gaze on the center of the screen (Fig. 1c).

2.4.1.2. Functional localizer task.
To localize the brain region in the LOTC that is sensitive to the upper limb (Orlov et al., 2010), we conducted a functional localizer task. In this task, the participants observed photographs of 5 different body parts (upper limbs, lower limbs, trunks, upper faces, and lower faces). We prepared a total of 60 photographs (12 photographs × 5 conditions = 60 photographs). The photographs were in gray scale, and the matrix size of all photographs was 3543 × 4724 pixels.

Each participant completed 2 runs that comprised 27 blocks each, 12 s per block. Each block was repeated 4 times in a run (5 conditions × 4 times = 20 blocks), and the other 7 blocks (1st, 2nd, 8th, 14th, 20th, 26th, and 27th blocks) were fixation-only baseline conditions. In each block, 6 photographs from 1 of the 5 object categories were successively presented for 1000 ms with a 1000 ms ISI, and each photograph was presented twice per run and 4 times per task (2 runs × 2 times = 4 times). As in the hand observation task, a fixation cross was presented during the baseline condition block and ISI of each condition, and the color of the fixation cross was changed from white to red for 1000 ms once per block. To hold the participants' gaze on the screen, they were asked to press a button with their right index finger when the red cross was presented.

2.4.2. Behavioral tasks

2.4.2.1. Assessment of the imitation difficulty in the ASD group.
The imitation ability in individuals with ASD was evaluated using the imitation task of Berges and Lézine (1965). The experimenter sat in front of the participant and made gestures using both hands, which the participant was required to imitate. After 24 gestures in total, the number of correct imitations was scored, and accuracy was calculated as the percentage of correct responses. Because of a technical problem, 1 individual with ASD did not complete the imitation task. The accuracy of the imitation task of individuals with ASD was 91 ± 9 (71–100) %.

2.4.2.2. Testing Self and Other hand identification ability.
To examine the ability to judge the identity of hands, we conducted the hand identification task under the same experimental setup as the hand observation task. During the hand identification task, 40 hand photographs used in the hand observation task were presented for 3000 ms with a 1000 ms ISI. The 40 images consisted of 8 photographs of own hands and 32 photographs of the hands of the 4 hand models, both sets including hand images from the first- and third-person perspectives. The participants were required to press a button with the index finger for their own hands, and another button with the middle finger for other person's hands. This behavioral task was performed before the fMRI experiments. The accuracy and response time (RT) of hand identification in each group were calculated.

2.5. fMRI data analysis

2.5.1. Preprocessing
The first 4 volumes of each run were discarded because of unsteady magnetization. The remaining 352 volumes (88 volumes × 4 runs) for the hand observation task and 208 volumes (104 volumes × 2 runs) for the functional localizer task were analyzed with the Statistical Parametric Mapping software (SPM12; Wellcome Department of Imaging Neuroscience, London, UK) implemented in MATLAB (MathWorks, Natick, MA, USA). After functional image realignment, we performed slice timing correction. Then, the high-resolution anatomical images were coregistered to the functional images. The images were normalized to a tissue probabilistic map fitted to the Montreal Neurological Institute (MNI) space via the segmentation-normalization process. The parameters from this segmentation-normalization process were then applied to all of the functional images, which were resampled to a final resolution of $2 \times 2 \times 2 \, mm^3$. The normalized fMRI images were filtered using a Gaussian kernel of 8 mm (full-width at half-maximum) in the x, y, and z axes.

2.5.2. Statistical analysis
We initially performed whole-brain analysis of the hand observation task to explore overall activation and then conducted a region of interest (ROI) analysis of the functionally defined ULS region in the LOTC, to test if brain activation related to hand identity and perspective was altered in individuals with ASD. Finally, we depicted the brain regions associated with the accuracy of the imitation task for individuals with ASD.

2.5.2.1. Whole-brain analysis of the hand observation task.
In individual analyses of the hand observation task, we fitted a general linear model to the fMRI data from each participant (Friston et al., 1994; Worsley and Friston, 1995). Neural activity was modeled with delta functions convolved with the canonical hemodynamic response function (HRF). Each run of the hand observation task included 11 regressors. Four regressors (S1, S3, O1, and O3) were modeled at the onset of each block, with a duration of 12 s. A fifth regressor was modeled for the participant's button press response for the red fixation-cross. Motion-related artifacts were modeled as regressors of no interest using the 6 parameters (3 displacements and 3 rotations) obtained by the rigid-body realignment procedure. The time series for each voxel was high-pass-filtered at 1/128 Hz. Assuming a first-order autoregressive model, the serial autocorrelation was estimated from the pooled active voxels with the restricted maximum likelihood (ReML) procedure and used to whiten the data. The parameter estimates for each condition in each individual were compared using linear contrasts.

In group analysis, we depicted the brain regions responsible for identity and perspective, and the brain regions showing significant differences between the ASD and TD groups. Contrast images of each condition (S1, S3, O1, and O3) relative to baseline from the individual analyses were used for the analysis. The contrast images obtained from the individual analyses represent the normalized task-related increment of the magnetic resonance signal of each participant. In order to implement the group analysis in a random-effects model, we utilized a 2 × 2 × 2 full factorial design (Identity × Perspective × Group). The Identity and Perspective factors were modeled as within-subject factors, and the Group factor was modeled as a between-subject factor.

We initially explored the brain regions showing 3-way interactions (Identity × Perspective × Group), 2-way interactions (Identity × Perspective, Group × Perspective, and Identity × Group), and main effects for each condition (Identity, Perspective, and Group) by F contrast. As F contrast does not provide information about the direction of activation, we performed a post-hoc analysis by T contrast to examine the activation pattern. The resulting set of voxel values for each contrast constituted the SPM{f} or SPM{t}. The statistical threshold for the spatial extent test on the clusters was set at p < 0.05 and corrected for

multiple comparisons at the cluster level over the whole brain (family-wise error), with a height threshold of p < 0.001 (Friston et al., 1996). Brain regions were anatomically defined and labeled according to a probabilistic atlas (Shattuck et al., 2008).

2.5.2.2. ROI analysis of the functionally defined ULS region in the LOTC. To avoid circular analysis (Kriegeskorte et al., 2010), we independently defined the ROI in the ULS area using a functional localizer task, and then evaluated the activation pattern of the hand observation task in the ROI. In individual analyses of the functional localizer task, each run included 12 regressors. Five regressors (upper limb, lower limb, trunk, upper face, and lower face) were modeled at the onset of each 12-s block. The other 7 regressors included the participant's button press response to the red fixation cross and 6 motion parameters. The other procedures of individual analysis were the same as in the hand observation task. Contrast images of upper limbs relative to the mean of the other 4 body parts (lower limb, trunk, upper face, and lower face) from the individual analyses were then used for the group analysis. Two-sample *t*-test was conducted on the contrast images in the ASD and TD groups. We used the same statistical threshold as in the hand observation task.

In the functionally defined ULS region in the LOTC for each group, we then evaluated the activation patterns of the 4 conditions (S1, S3, O1, and O3) of the hand observation task. The parameter estimates of the 4 conditions (S1, S3, O1, and O3) relative to fixation-only baseline conditions were extracted from the peak coordinates of the ULS region in the LOTC for each group. We examined the activation pattern in the ULS region by conducting 3-way analysis of variance (ANOVA) (Identity × Perspective × Group) and post-hoc pairwise comparisons of the parameter estimates using the SPSS statistics software.

2.5.2.3. Depicting the brain region associated with the imitation ability in individuals with ASD. We depicted the brain region associated with the accuracy of the imitation task in the individuals with ASD. The contrast

images of perspective-dependent activation (S3 + O3)–(S1 + O1), identity-dependent activation (S1 + S3)–(O1 + O3), and the interaction of perspective and identity (S1 − S3)–(O1 − O3) of the 17 individuals with ASD were used for the analysis. We used the 1-sample *t*-test on each contrast image and entered the accuracy of imitation as a covariate. Using T contrast, we depicted the brain region associated with imitation difficulties. We used the same statistical threshold as that in the hand observation task.

3. Results

3.1. Behavioral performance on the hand observation and functional localizer tasks

We compared the behavioral performance on both the hand observation and functional localizer tasks between the ASD and TD groups (Additional Table 1). The mean accuracy was above 99% for both tasks in both groups. Independent-samples *t*-tests revealed no group differences in accuracy and RT for both tasks (all p > 0.1). These findings suggest that both groups responded similarly to visual stimuli in the tasks.

### 3.2. Whole-brain analysis of the hand observation task

We initially explored overall activation patterns in the hand observation task: the main effects and interactions of Identity, Perspective, and Group.

3.2.1. Interactions

The F contrast of the interaction of 3 factors (Identity × Perspective × Group) revealed no significant activation (Additional Table 2).

The F contrast of the Group × Perspective interaction revealed significant activation in the medial prefrontal cortex (mPFC), which covers the middle frontal gyrus (MFG) and anterior cingulate gyrus
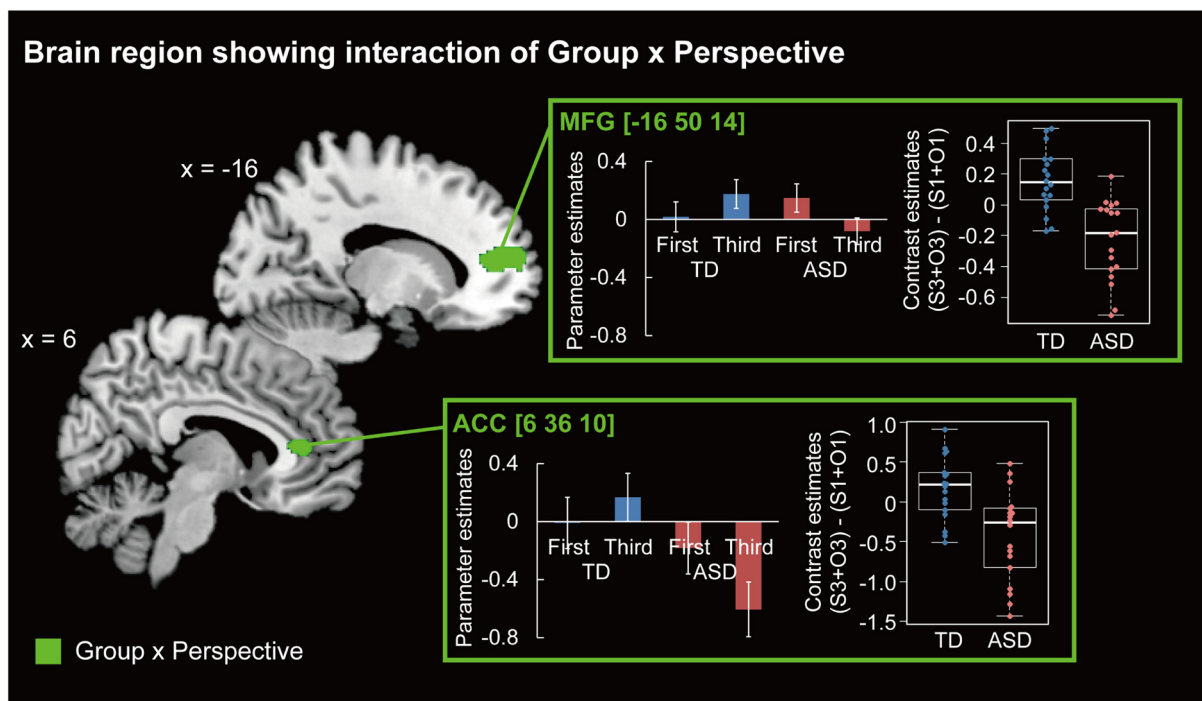
Fig. 2. Whole-brain analysis: interaction of Group and Perspective.
TD: Typically developing, ASD: Autism spectrum disorder, ACC: Anterior cingulate cortex, MFG: Middle frontal gyrus, Brain region showing the F contrast of the interaction of Group × Perspective superimposed on a T1-weighted magnetic resonance image. The size of activation was set at a threshold of p < 0.05 and corrected for multiple comparisons, with the height threshold set at p < 0.001. First indicates the mean parameter estimates of S1 and O1. Third indicates the mean parameter estimates of S3 and O3. Error bars indicate the standard error of the mean (SEM).

Table 2
Whole-brain analysis by T contrast.

Cluster		Peak					
p-Values	Size	T values	MNI coordinate			Hem	Region
	(mm^3)		x	y	z		
Brain region showing interaction							
Interaction of Group and Perspective							
TD (third vs. first) > ASD (third vs. first)							
< 0.001	6272	5.15	−16	50	14	L	Middle frontal gyrus
		6	36	10		R	Cingulate gyrus
ASD (third vs. first) > TD (third vs. first)							
n.s.							
Brain region showing main effect							
Main effect of identity							
Self vs. Other							
< 0.001	16,936	6.78	−30	−88	−10	L	Inferior occipital gyrus
		4.63	−36	−60	−10	L	Lingual gyrus
< 0.001	16,416	6.04	28	−76	2	R	Inferior occipital gyrus
		5.33	34	−54	−16	R	Fusiform gyrus
Other vs. Self							
n.s.							
Main effect of Perspective							
First vs. third							
< 0.001	19,848	51.90	8	−78	−4	R	Lingual gyrus
		48.64	−6	−80	−8	L	Lingual gyrus
		31.84	−18	−76	−10	L	Inferior occipital gyrus
Third vs. first							
< 0.05	2504	41.17	−10	−100	6	L	Middle occipital gyrus
< 0.05	2880	39.67	16	−98	10	R	Middle occipital gyrus

TD: Typically developing, ASD: Autism spectrum disorders, Hem: Hemisphere, R: Right, L: left, n.s.: Not significant. The statistical threshold was set at p < 0.05, corrected for multiple comparisons at the cluster level, with a height threshold of p < 0.001. First indicates first-person perspective conditions (S1 and O1) and Third indicates third-person perspective conditions (S3 and O3). Self indicates self conditions (S1 and S3) and Other indicates other-person conditions (O1 and O3).

(ACC) (Additional Table 2, Fig. 2). In order to characterize the activation pattern, we compared the effect of the third-person perspective (relative to the first-person perspective) between the 2 groups using T contrast. As compared with the ASD group, the TD group revealed significantly stronger activation in the mPFC, including the MFG and ACC. No stronger activation was found in the ASD group compared with the TD group (Table 2).

The F contrast of the Identity × Perspective or Identity × Group interaction revealed no significant activation (Additional Table 2).

3.2.2. Main effects

The F contrast for the main effect of Identity revealed significant activation in the bilateral inferior occipital gyrus (IOG), left lingual gyrus, and right fusiform gyrus (Additional Table 2). The T contrast of the Self conditions against the Other conditions revealed activation in the bilateral IOG, the left lingual gyrus, and the right fusiform gyrus (Table 2; Additional Fig. 1). In contrast, Other vs. Self conditions showed no significant activation.

The F contrast for the main effect of Perspective revealed significant activation in the bilateral lingual gyrus, left IOG, and bilateral middle occipital gyrus (MOG; Additional Table 2). The T contrast of the first-person perspective relative to the third-person perspective conditions revealed activation in the bilateral lingual gyrus and left IOG. In contrast, the T contrast of the third-person perspective relative to the first-person perspective conditions revealed activation in the bilateral MOG (Table 2, Additional Fig. 1).

The F contrast of the main effect of Group revealed no significant activation (Additional Table 2).

Collectively, the whole brain analyses revealed that the mPFC showed different activation between the ASD and TD groups; activity in the third-person perspective relative to the first-person perspective was significantly greater in the TD group as compared with that in the ASD group.

3.3. ROI analysis in the ULS area of the LOTC

We then conducted the ROI analysis to test our hypothesis in the functionally defined ULS region. We initially defined the ULS region for each group by evaluating the T contrast of the upper limb vs. the mean of the other body parts in the functional localizer task. The bilateral ULS regions were identified in the ASD group (x = 44, y = −62, z = 4 for the right hemisphere; x = −50, y = −64, z = 2 for the left hemisphere) as well as in the TD group (x = 58, y = −64, z = 6 for the right hemisphere; x = −54, y = −70, z = 4 for the left hemisphere) (Fig. 3a). T contrasts revealed no significant group differences, which indicates comparable upper-limb-sensitive activation between the ASD and TD groups.

In order to evaluate activity in the ULS region during the hand observation task, we extracted activity (parameter estimates) at peak coordinates. A 3-way ANOVA (Identity × Perspective × Group) of activity in the right ULS region revealed neither a significant interaction nor a main effect (all p > 0.1). In contrast, the same 3-way ANOVA of activity in the left ULS region revealed a significant Group × Perspective interaction [F(1,34) = 4.75, p < 0.05]. No other significant effect was found (all p > 0.1). Post-hoc pairwise comparison with the Bonferroni correction revealed that activation in the third-person perspective condition was significantly stronger than that in the first-person perspective in the TD group (p < 0.05). In contrast, there was no such difference in the ASD group (p > 0.6) (Fig. 3b).

### 3.4. Brain regions correlated with imitation task accuracy in the ASD group

We depicted the brain regions showing correlation with imitation task accuracy in the ASD group. The perspective-dependent activation (S3 + O3) − (S1 + O1) in the bilateral IPL and cerebellum was significantly correlated with the accuracy of imitation, whereas identity-dependent and interaction-dependent activation did not show

a. Upper limb sensitive region in the LOTC for each group
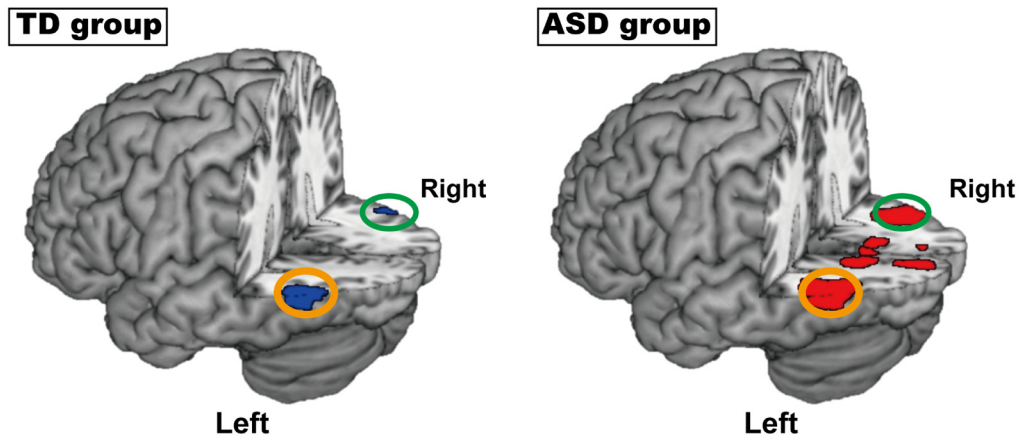
b. Activation by the hand observation task in the upper limb sensitive region
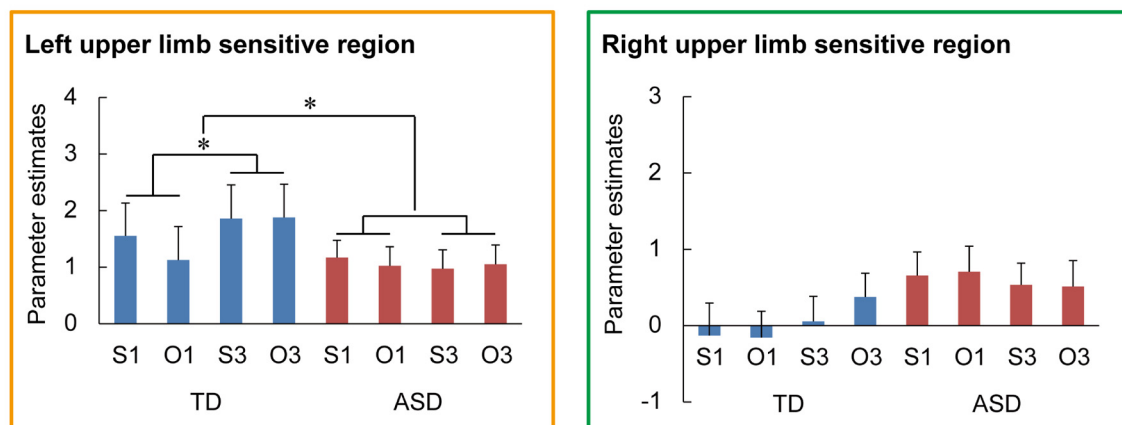
Fig. 3. Brain activation in the upper-limb-sensitive (ULS) area during the hand observation task.
(a) A region of interest (ROI) was placed on the ULS region of the lateral occipito-temporal cortex (LOTC). The ROIs for the TD and ASD groups determined by the functional localizer task were superimposed on a T1-weighted magnetic resonance image. The size of the activation was set at a threshold of $p < 0.05$ and corrected for multiple comparisons, with the height threshold set at $p < 0.001$, to localize the ULS region of the LOTC. (b) Activation pattern (contrast estimates) during the hand observation task was extracted at the peak coordinates of the functionally defined ULS region. Error bars indicate the standard error of the mean, and * indicates $p < 0.05$.

association with imitation task accuracy (Table 3, Fig. 4).

3.5. Head motion during the hand observation task

As head motion can affect fMRI results, we compared the motion parameters of 3 displacements (x, y, and z axes) and 3 rotations (pitch, roll, and yaw) between the ASD and TD groups. Specifically, we calculated (1) the difference in the maximum and minimum values of each parameter within a run and (2) the SD of the time-series values of each parameter within a run. Additional Table 3 shows the means of these values in the 4 runs. An independent-samples t-test revealed no significant differences between the 2 groups in all values (all $p > 0.2$). We then examined correlations between the regressors of each condition (S1, S3, O1, and O3) and the 6 motion parameters for the 2 groups (Additional Table 4). An independent-samples t-test revealed no significant differences between the 2 groups (all $p > 0.05$).

3.6. Self and Other's hand identification ability in each group

We also tested the hand identification ability of each group by conducting an additional behavioral experiment (the hand

identification task). Three-way ANOVA (Identity × Perspective × Group) of the accuracy of the hand identification task showed significant interaction of Identity and Perspective [$F(1,33) = 18.1$, $p < 0.001$] and a main effect of Perspective [$F(1,33) = 24.1$, $p < 0.001$]. Post-hoc pairwise comparison with the Bonferroni correction revealed a significant difference between the S3 and O3 conditions ($p < 0.05$), whereas there was no significant difference between the S1 and O1 conditions ($p > 0.9$). The main effects of Identity and Group, and the Group × Perspective, Identity × Group, and Identity × Perspective × Group interactions were not significant (all $p > 0.1$) (Additional Table 5).

The same 3-way ANOVA of RT revealed a significant Group × Perspective interaction [$F(1,33) = 4.2$, $p = 0.04$], and main effects of Perspective [$F(1,33) = 18.3$, $p < 0.001$] and Identity [$F(1,33) = 9.8$, $p = 0.004$]. Post-hoc pairwise comparison with the Bonferroni correction revealed a significant difference between the first-person and third-person perspective conditions in the TD group ($p < 0.001$), whereas there was no perspective effect in the ASD group ($p > 0.2$). The Identity × Group, Identity × Perspective, and Identity × Perspective × Group interactions, and the main effect of Group were not significant (all $p > 0.1$) (Additional Table 5). In the

Table 3
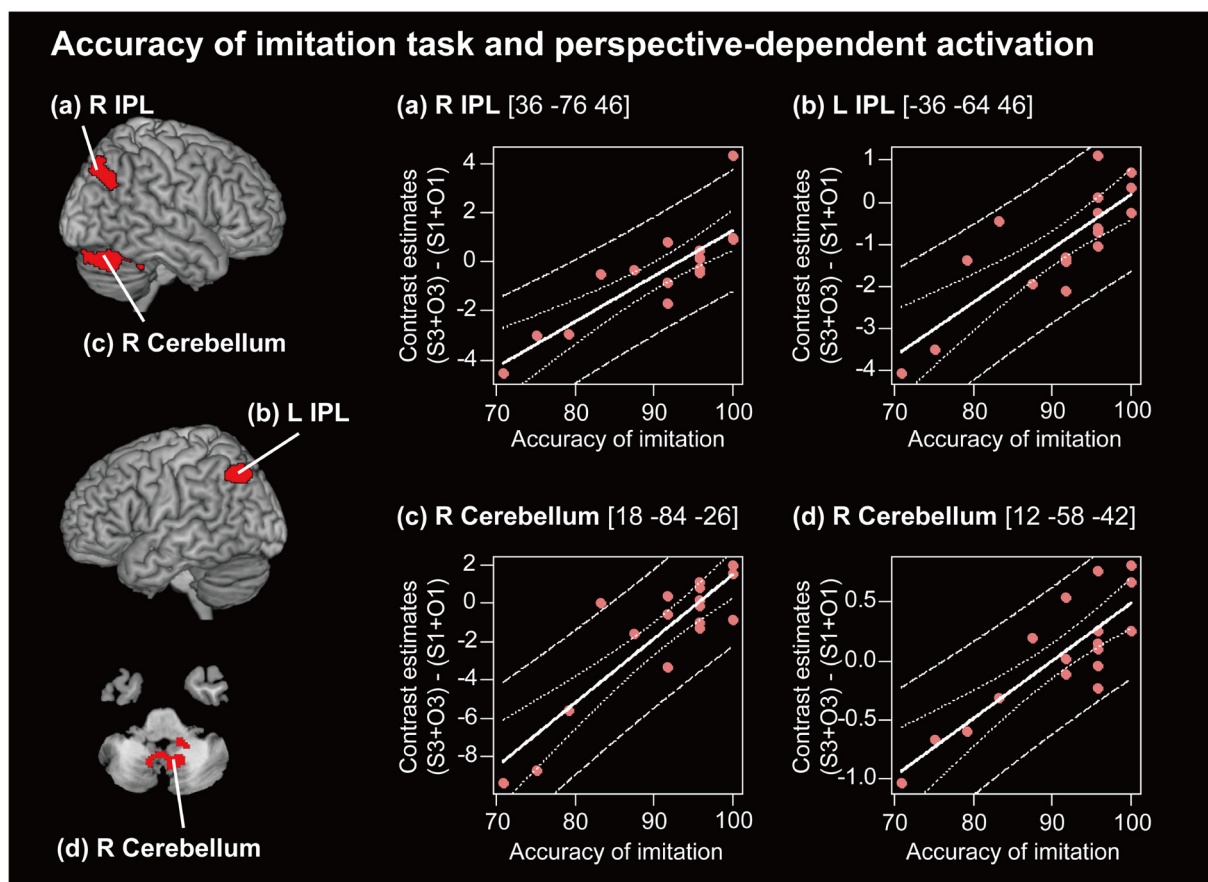Brain regions showing significant correlation with imitation accuracy in the ASD group.

Cluster		Peak					
p values	Size	T values	MNI coordinate			Hem	Region
	(mm³)		x	y	z		
Brain region correlated with imitation accuracy							
Perspective (S3 + O3)–(S1 + O1)							
< 0.001	3736	7.16	18	− 84	− 26	R	Cerebellum
< 0.01	3304	6.08	12	− 58	− 42	R	Cerebellum
		5.35	− 6	− 54	− 46	L	Cerebellum
< 0.05	1936	5.98	36	− 76	46	R	Inferior parietal lobule
< 0.05	1880	5.59	− 36	− 64	46	L	Inferior parietal lobule
Identity (S1 + S3)–(O1 + O3)							
n.s.							
Interaction of Perspective and Identity (S1 − S3)–(O1 − O3)							
n.s.							

Hem: Hemisphere, R: Right, L: Left, n.s.: Not significant. The statistical threshold was set at p < 0.05, corrected for multiple comparisons at the cluster level, with a height threshold of p < 0.001.

whole-brain analysis, neither the ASD nor TD group showed a significant correlation between the perspective-dependent activity and the corresponding effect in RT (i.e., contrast estimates and RT calculated as (S3 + O3)–(S1 + O1)). Similarly, we found no such correlation in the ULS region in the ROI analysis (all values p > 0.4).

Collectively, the accuracy of hand ownership identification was similar between the ASD and TD groups. In contrast, the effect of Perspective on RT was attenuated in the ASD group as compared with the TD group, which was similar to the activation pattern in the left ULS region.

Fig. 4. Brain regions showing significant correlation with the imitation accuracy in individuals with autism spectrum disorder (ASD).
The brain region showing significant correlation with the accuracy of the imitation task was superimposed on a T1-weighted magnetic resonance image. The size of the activation was set at a threshold of p < 0.05 and corrected for multiple comparisons, with the height threshold set at p < 0.001. Correlations between activation and each score at each peak coordinate were plotted in a, b, c, and d. The regression line is represented by a straight line. Confidence intervals and prediction intervals are represented by dotted lines and broken lines, respectively.

4. Discussion

In the present study, we examined if the effects of identity and perspective on the response to observed hands in the ULS region of the LOTC were different between individuals with and without ASD. We found that the perspective effects in the left ULS region and mPFC were different between the ASD and TD groups. We further found that the imitation performance of individuals with ASD correlated with perspective-dependent activation in the bilateral IPL and cerebellum.

4.1. Attenuated perspective effect in the left ULS region of individuals with ASD

In the present study, the left ULS region showed a stronger response to hands observed from the third-person perspective than from the first-person perspective, consistent with previous studies of TD individuals (Chan et al., 2004; Saxe et al., 2006). The first-person perspective is not always necessary for self-body recognition, as we recognize our faces in the third-person perspective (in mirrors or pictures). However, the first-person perspective is highly associated with the recognition of one's own hands, because we usually observe our own hand in the first-person perspective. Thus, the perspective can influence several cognitive functions, including self-body or self-action recognition. Behavioral performance in hand identification was influenced by the hand observation perspective in the present study, which is consistent with a previous finding that the judgment of whether a visually presented hand is the right or the left hand is affected by perspective (Kitada et al., 2010). In addition, it has been suggested that the perspective of the body contributes to the sense of agency (i.e., the sense that an action is caused by oneself) (David et al., 2008; review). Thus, it is reasonable to assume that the first-person perspective constitutes an important factor contributing to the recognition of one's own body parts such as hands. In this sense, the perspective-sensitive activation in the ULS region of the LOTC is relevant for visual processing for self-body recognition. In addition, a meta-analysis showed involvement of the left LOTC in various social functions, namely the false-belief and visual-perspective-taking tasks (Schurz et al., 2013). Specifically, Schurz et al. (2013) found overlapped activation in the LOTC in the visual-perspective-taking and false-belief tasks, and proposed that the overlapped activation might be caused by imagined body transformations when another person's viewpoint was adopted. Thus, it is possible that the left LOTC in TD individuals is involved in social interaction as well as visual self-body recognition.

The novel finding of the present study is that, unlike in TD participants, this perspective effect in the left ULS region was not observed in ASD participants. One possible explanation is that this difference reflects different patterns of attention to presented hands. If this is the case, the early visual area should also show similar group-dependent activation (Bressler et al., 2013; David et al., 2007; Myers and Sowden, 2008). However, the early visual area did not show interaction of perspective and group (Additional Fig. 1). In addition, there was no group difference in the response to the presentation of the red cross during the hand observation task. Thus, it is unlikely that the attenuation of the perspective effect in the LOTC of individuals with ASD is caused by a difference in attentional patterns. Alternatively, we found that the response time to judge hand identity was altered by the hand perspective in the TD group, whereas such effect was attenuated in the ASD group. Thus, it is more reasonable to interpret that the difference in the perspective effect between the groups reflects altered processing of self-hand recognition in ASD individuals. Neither the TD nor ASD group showed a correlation between the activity of the ULS region in the hand observation task and behavioral performance in the hand identification task. One possibility is that the inter-individual differences in brain activity were small within each group. Indeed, in the ASD group, the standard deviations (SDs) of parameter estimates of Third-person perspective vs. First-person perspective in the left ULS and mPFC

were 0.70 and 0.26, respectively. These SDs were smaller than those in the cerebellum (1.70) and IPL (1.02), which were correlated with imitation difficulties in ASD participants. It is possible that the absence of a perspective effect in the LOTC and mPFC might be a common core feature among individuals with ASD.

Further, this alteration might be associated with the atypical self-body awareness and social interaction in ASD individuals. This speculation is supported by the following 2 points from previous studies. First, in TD individuals, the LOTC is active during the rubber hand illusion, in which participants feel the dummy hand as their own hand (Limanowski et al., 2014). Individuals with ASD experience the rubber-hand illusion differently from TD individuals, indicating altered body ownership (Cascio et al., 2012; Paton et al., 2012). Second, one of the characteristics of ASD is difficulty in performing theory-of-mind and visual-perspective-taking tasks (Baron-Cohen, 1997; Conson et al., 2015; Hamilton et al., 2009). The LOTC of individuals with TD is involved in the false-belief and visual-perspective-taking tasks (Schurz et al., 2013), whereas activity of the LOTC of individuals with ASD is atypical during the theory-of-mind task (Kirkovski et al., 2016). Thus, altered response to hands in different perspectives might reflect a more primitive mechanism that could explain the atypical self-body awareness and difficulty of social interaction in individuals with ASD.

4.2. Function of the LOTC in ASD

The LOTC is known to have various functions, including in bodily interactions (Kret et al., 2011: Okamoto et al., 2014; Peelen et al., 2007; Vangeneugden et al., 2014; Wiggett and Downing, 2011), categorization of body parts (Bracci et al., 2010; Downing et al., 2001; Orlov et al., 2010; Peelen and Caramazza, 2010), and visual self-body recognition (Chan et al., 2004; Myers and Sowden, 2008; Saxe et al., 2006). For instance, with regard to bodily interactions, the LOTC is responsible for understanding body actions (Vangeneugden et al., 2014; Wiggett and Downing, 2011), mental states (e.g., emotions) implied in actions (Kret et al., 2011; Peelen et al., 2007), and detecting contingency between executed and observed actions (Okamoto et al., 2014). Which LOTC function is altered in adults with ASD? In the present study, the LOTC showed an atypical response to hands presented in different perspectives for adults with ASD, although the function of categorizing body parts was likely intact (Okamoto et al., 2014, 2017). Furthermore, a previous study found atypical activation in the LOTC while viewing emotional bodily action in adults with ASD (Hadjikhani et al., 2009). Thus, it is possible that higher-order LOTC functions, rather than simple categorization of body parts (i.e., processing body ownership or actions) are different between TD and ASD adults.

These atypical functions of the LOTC in adults with ASD can lead to different activation patterns in other brain regions, such as the STS and lateral fronto-parietal cortices. It is known that the LOTC is functionally connected to the STS and fronto-parietal cortices, which is critical for action understanding and bodily interactions (Gazzola and Keysers, 2009; Sasaki et al., 2012; Taylor et al., 2007). For instance, dynamic causal modeling of fMRI data showed that the effective connectivity of the LOTC to the lateral frontal cortex, via the STS, was enhanced when participants observed an action (e.g., manipulating balls with their right hands) (Sasaki et al., 2012). Previous studies have shown that the LOTC processes body form (i.e., the static feature of action), whereas the STS processes body motion (i.e., the dynamic feature of action) (Vangeneugden et al., 2014; Downing et al., 2006), both of which are relevant for action understanding (Takahashi et al., 2008; Kable and Chatterjee, 2006). Thus, it is possible that the static features of observed body images represented in the LOTC are sent to the STS for processing dynamic action features, which are then further processed in the frontoparietal region.

If the visual features of bodies are processed differently in the LOTC, the fronto-parietal regions and STS may also show an atypical response

in ASD. Indeed, previous fMRI studies have reported that activation in the posterior STS was attenuated in individuals with ASD when they observed biological motion (Pelphrey and Carter, 2008; Yang et al., 2017). Thus, the attenuated response in the STS may be associated with abnormal representation of dynamic aspects of actions, whereas the abnormal activity in the LOTC may be associated with abnormal representation of static action forms. Furthermore, atypical activation in the lateral frontal cortex in individuals with ASD during imitation was also reported (Dapretto et al., 2006). In the future, it is important to examine how altered visual processing in the LOTC is associated with the atypical response to body perspective or bodily action in the lateral fronto-parietal cortices and STS.

4.3. Attenuated perspective effect in the mPFC of individuals with ASD

In addition to the LOTC, the mPFC also showed distinctive perspective effects in the ASD and TD groups. In contrast to our present study, previous fMRI studies of TD individuals did not show such perspective-dependent activation in the mPFC when participants passively observed their whole body or various body parts (e.g., hand and foot) (Chan et al., 2004; Saxe et al., 2006). One of the main differences between the present and previous studies is in the body pictures used as visual stimuli: our study was limited to hand pictures whereas the other studies showed various body parts in the same experiment (e.g., hand and foot) (Chan et al., 2004; Saxe et al., 2006). Thus, it is possible that perspective-dependent activation in the mPFC is more prominent when the body is restricted to specific body parts such as hands. Moreover, no previous study has examined perspective-dependent brain activation while viewing the body in individuals with ASD. Thus, our finding of altered perspective-dependent activation in the mPFC of ASD individuals is novel.

Previous studies have shown that the cortical midline structure (CMS) including the mPFC is involved in self-representation (Iacoboni, 2006; Northoff et al., 2011; Sugiura, 2013; Uddin et al., 2007). In particular, the CMS is associated with the psychological self, which is distinct from the lateral fronto-parietal and occipito-temporal cortices representing the physical self (Iacoboni, 2006; Sugiura, 2013; Uddin et al., 2007). However, a recent activation likelihood estimation (ALE) meta-analysis provided evidence against the above-mentioned function of the CMS (Hu et al., 2016). Specifically, Hu et al. (2016) examined common and distinctive brain activation during an self-face recognition task (a representative task of the physical self) and during a self-referential task (a representative task of the psychological self). The ACC within the mPFC was activated during both tasks, indicating that the ACC might be associated with the core self (Hu et al., 2016). Furthermore, the involvement of the ACC in the physical self is also supported by studies of patients with eating disorders. Specifically, patients with anorexia nervosa, who are characterized by having distorted own-body images (DSM-5; American Psychiatric Association, 2013), showed atypical activation in the ACC as well as the LOTC when they observed pictures of human bodies (Gaudio et al., 2015; Suchan et al., 2013). These findings suggest that the ACC, a part of the CMS, is involved in the physical self as well as the psychological self. Therefore, it is reasonable to conclude that the ACC is responsible for hand perspective processing. Our findings suggest that atypicality of the ACC representing the core self, along with the LOTC representing the physical self, may also be the neural underpinning of atypical self-body awareness in individuals with ASD.

4.4. Perspective effect in the IPL and cerebellum correlates with imitation accuracy in individuals with ASD

We further found that perspective-dependent activation in the bilateral IPL and cerebellum, but not in the LOTC, was associated with the accuracy of the imitation task. Previous fMRI studies have suggested that the IPL and cerebellum are involved in visual processing of body

perspective (David et al., 2006; Jackson et al., 2006). Furthermore, several studies have reported that both regions are involved in imitating another person's actions. An ALE meta-analysis of fMRI studies of TD individuals showed that the IPL was consistently activated when participants imitated another person's actions (Caspers et al., 2010; Molenberghs et al., 2009). In particular, the IPL is thought to play a role in adopting another person's perspective during imitation (Oh et al., 2012). The IPL is also involved in aspects of the physical self such as the body schema (Branch Coslett et al., 2008; Medina et al., 2009; Blanke et al., 2005) and the sense of agency (Decety and Grèzes, 2006; David et al., 2007), and in social interaction such as perspective taking (Vogeley and Fink, 2003; Wang et al., 2016) and the theory of mind (Van Overwalle, 2011; Schurz et al., 2013; Bögels et al., 2015). Furthermore, several studies have reported connectivity of the LOTC and IPL (David et al., 2007 for the sense of agency; Sasaki et al., 2012 for imitation). These findings suggest that visual information of body perspectives processed in the LOTC might also be sent to the IPL, one of the important hubs of the network. The cerebellum is thought to be connected with the mirror neuron system (MNS) (Gazzola and Keysers, 2009) and is involved in imitation (Jackson et al., 2006; Oh et al., 2012). For instance, Jackson et al. (2006) showed that activation of the cerebellum is enhanced by imitating gestures observed from the third-person perspective relative to the first-person perspective in TD individuals. Thus, it is reasonable to conclude that perspective representation in the bilateral IPL and cerebellum contributes to the imitation abilities of ASD participants and might be one of the neural mechanisms of heterogeneity in individuals with ASD.

In fact, previous fMRI studies examining brain activation during hand gesture imitation by individuals with ASD reported both altered and equivalent activation in the IPL and cerebellum. For instance, fMRI studies of younger individuals with ASD (i.e., children and adolescents) showed atypical activation in the posterior parietal cortex during imitative hand movement (Wadsworth et al., 2017; Williams et al., 2006) and association of the functional connectivity between the LOTC and cerebellum with the theory-of-mind ability (Jack and Morris, 2014). Unlike in these studies, there was no atypical activation in adults with ASD when they imitated hand gestures (Okamoto et al., 2014). This discrepancy may be explained by differences in the age of the participants. Previous behavioral studies have found improvement of imitation skills throughout development (Beadle-Brown and Whiten, 2004; Young et al., 2011). In the present study, 3 of 17 individuals with ASD successfully imitated all gestures. Therefore, it is possible that the functions of the IPL and cerebellum are improved throughout development, ultimately reaching normal levels in several individuals with ASD. Thus, it is reasonable to conclude that some but not all individuals with ASD remain impaired in the IPL and cerebellum, which process body perspectives, providing an explanation why they still have difficulty imitating another person's actions when they become adults.

4.5. Limitations and further studies

We should note three limitations of the present study. First, as described above, we did not examine how reduced perspective-related activation in the LOTC affects activation in the other brain regions, including the lateral fronto-parietal cortices, during bodily interaction. Second, we only measured the imitation ability in individuals with ASD but not in TD individuals, because we aimed to investigate the heterogeneity of ASD. However, further study examining the association of the imitation ability and perspective-related brain activation in individuals with TD should be helpful for a better understanding of the general neural mechanisms underlying imitation skills. Third, we did not compare brain activity during the observation of "palm-up images" and "back-of-the-hand" images, as the task design was not optimized for such comparisons. It is worth examining the effect of the participant's posture on brain activity in our task, as congruent postures (e.g., those of hands) can generate better imitation performance (Brass et al.,

2001; Kessler and Miellet, 2013; Miall et al., 2006; Stürmer et al., 2000).

5. Conclusion

In the present study, we examined if activation in the LOTC associated with body perspective and identity is altered in individuals with ASD. Perspective-dependent activation in the left ULS region of the LOTC and mPFC was attenuated in the ASD group compared with that in the TD group. Furthermore, the imitation skills of individuals with ASD might predict perspective-dependent activation in the bilateral IPL and cerebellum. These findings shed light on the pathophysiology and nature of heterogeneity of ASD.

Ethics approval and consent to participate

Our protocol was in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the University of Fukui (Japan). Before participation, written informed consent was obtained from each participant. All methods were carried out in accordance with the approved protocol.

Consent for publication

We received consent for publication of the hand pictures shown in Fig. 1.

Availability of data and material

The datasets generated and analyzed during the current study are not publicly available because reuse of the data was not intended when we received approval from our ethics committee.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YO conceived of the study, acquired, analyzed, and interpreted data, and drafted the manuscript. RK conceived of the study, helped to analyze and interpret data, and drafted the manuscript. MM helped to acquire and interpret data, and draft the manuscript. TK helped to analyze data. HN acquired data. NS helped to interpret data. HO helped to acquire data. HK acquired data and helped to draft the manuscript. All authors read and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2018.04.030.

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